RESEARCH

Research Editorial

Diet and Survival after Ovarian Cancer: Where Are We and What's Next?

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THE PROBLEM

The prognosis after epithelial ovarian cancer treatment remains dismal. It is estimated that 21,500 women will be diagnosed with ovarian cancer in 2009; 14,600 will die of their disease, making ovarian cancer among the most lethal of cancer diagnoses (1). Whereas ovarian cancer accounts for only 3% of new cancer cases, it represents 5% of total cancer deaths in the United States with a reported 5-year overall survival rate for all stages of disease of 45.5%. Early detection continues to be a major challenge and explains much of the mortality because women diagnosed with local disease demonstrate a 92% survival rate. There are no strong risk factors for ovarian cancer; however, age, nulliparity, family history, previous diagnosis of breast cancer, estrogen therapy, and genetic variants in BRCA1 and 2 have been associated with greater risk. Regarding *modifiable* risk factors, diet, physical activity, and body mass index (BMI) hold promise for reducing the incidence of this disease.

The role of diet and specific dietary constituents in the development of or survival from ovarian cancer is not clearly understood (2). Recently, an analysis of results from the Women's Health Initiative study of 48,835 postmenopausal women in the Diet Modification trial suggested that long-term (8.1 years) reduction in dietary fat was associated with a significant 40% reduction in ovarian cancer risk (3). Although this is the only prospective intervention trial evaluating the role of diet in ovarian cancer prevention, this was a secondary analysis of a trial targeting breast cancer risk reduction. Certainly, several planned epidemiological studies have suggested that high fat intake, high animal protein intake, and higher total energy intake as well as a Western diet are associated with an increased risk for this disease (4-12), as has the

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World Cancer Research Fund/American Institute of Cancer Research comprehensive report on the epidemiological evidence (13).

DIET AND SURVIVAL

Few studies have evaluated the association between diet and ovarian cancer survival. The few that have evaluated this association have focused on diet before or at the time of diagnosis, not the impact of diet change after diagnosis. In a case-control study by Nagle and colleagues, total and saturated fat were shown to adversely affect ovarian cancer outcome, with hazard ratios ranging from 1.06 to 1.32 (14). Nagel also reported a protective association for higher cruciferous vegetable intake, and a protective role for green tea has also been suggested (15). More efforts to assess these associations using existing epidemiological datasets, specifically in the United States, are warranted.

Beyond the role of diet in modifying risk for cancer recurrence, several reports have evaluated diet as a risk factor for mortality. In fact, prediagnosis diet may influence mortality even more than it impacts recurrence of cancer. For example, a 46% reduction in overall mortality ($P=0.05$) and a 44% reduction in cancer recurrence ($P=0.08$) (16) was shown in relation to higher vegetable intake among subjects diagnosed with oral cancer. Similarly, a 43% reduction in overall mortality was shown in the Life After Cancer Epidemiology (LACE) study of breast cancer survivors in relation to intake of a prudent, vegetable- and whole-grain–rich diet (hazard ratio=0.57, 95% confidence interval [CI] 0.36 to 0.90) (17). Whereas the Wheat Bran Fiber trial (18) and Polyp Prevention Trial (19) showed no significant reduction in adenoma recurrence with dietary interventions except among those reporting strict adherence to the high-vegetable and -fruit diet of the polyp prevention trial (20). An analysis of prediagnosis diet among colorectal cancer survivors suggested those with the highest Western diet score had a hazard ratio for disease-free survival of 3.25 (95% CI 2.04 to 5.19) and of 2.85 (95% CI 1.75 to 4.63) for recurrence-free survival (21). These studies reinforce the need to promote a cancer-preventive diet throughout life to improve post-treatment survival.

In the report from Dolecek and colleagues in this month's edition of the *Journal* (22), the authors provide new evidence that dietary factors, particularly total fruit and vegetable, red and processed meat, and milk intakes, may influence ovarian cancer survival. These findings corroborate earlier work by Nagel and colleagues (14) and are among only a select few studies of dietary associations with ovarian cancer recurrence and/or prognosis.

Although the study by Dolecek and colleagues is observational and, thus, carries all the well-described limita-

tions of observational research, including an inability to test causation, the findings suggest that prediagnosis dietary patterns are associated with improved progression-free survival for ovarian cancer. This is important because it suggests that adult habits or even lifelong dietary habits, although not always effective in preventing ovarian cancer, may establish a host environment that promotes response to cancer treatment (22). These data are consistent with emerging evidence from other cancer studies, including the Women's Healthy Eating and Living Study, a large randomized dietary intervention trial that showed no reduction in breast cancer recurrence risk with adoption of a plant-based diet on average 2.3 years after treatment for early stage invasive breast cancer. In this study significant protective associations were shown for "usual" dietary patterns before randomization that were higher in vegetables and fruit and more specifically were associated with higher plasma carotenoid concentrations. Importantly, "healthful" dietary patterns in this study, as well as most, are highly correlated with other behaviors such as physical activity, moderation in alcohol intake, lower rates of tobacco use (23), and lower BMI. These congregate behaviors are likely to promote improved immunity, reduced inflammation, and lower endogenous reactive oxygen species and associated DNA damage in the host that may explain the observed protective associations.

WEIGHT GAIN A SUBSEQUENT RISK

Body weight was not a specific focus of the Dolecek analysis, but numerous reports in the breast cancer literature suggest that pre- and post-diagnosis weight gain and adiposity is associated with poorer prognosis, and body weight is a significant confounder in most dietary studies. There is limited evidence evaluating the role of weight change and ovarian cancer survival (24). A few studies have evaluated the role of body weight in relation to progression-free survival in women diagnosed and treated for ovarian cancer. In 2006, Pavelka showed median survival of 80 months among women presenting at ideal body weight vs 62 months among those who met diagnostic criteria of obesity (BMI >30) (25). Although the finding of Pavelka and colleagues was clinically relevant, the P value of 0.3 was not statistically significant, possibly due to the small sample size (n=216) (25). However, more recent evidence suggests that when debulking surgery and adjuvant therapies are equivalent, the 5-year survival is not different for obese vs nonobese women (26-28). A prospective study by Yang and colleagues (29) showed that being overweight in recent years (in relation to ovarian cancer diagnosis) for women with International Federation of Gynecology and Obstetrics stage I,II disease was associated with greater post-treatment mortality. Evaluation of the relationship between diet and ovarian cancer survival will require consideration for concomitant effects of body weight because weight and related factors are likely to influence interpretation of the results.

TIME TO FILL THE RESEARCH GAPS

Most concerning is the lack of prospective trials among ovarian cancer survivors to test the efficacy of lifestyle and behavior-based interventions to improve clinical response, disease-free survival, or overall mortality. In fact, no data exist. Given the mounting evidence from a variety of cancers, it seems prudent to test interventions of this nature. Ideally, ovarian cancer survivors would be recruited into such a trial using a healthful diet pattern as a stratifying variable. In this way, we could evaluate the independent effects of prediagnosis diet and postdiagnosis adoption of a healthful diet to determine whether adoption of a healthful diet must occur before diagnosis, as much of the current evidence suggests, or whether a marked improvement in eating patterns (possibly combined with physical activity) after diagnosis would suffice in modifying cancer recurrence and overall mortality. The time has come to test these hypotheses and to potentially impact the health of thousands of women diagnosed with ovarian cancer each year.

STATEMENT OF POTENTIAL CONFLICT OF INTEREST: The authors have no conflict of interest to report.

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